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Respiratory Medicine (2006) **100**, 363–366

respiratoryMEDICINE

SHORT COMMUNICATION

Ecological association between scarlet fever and asthma

Mario H. Vargas[a,b,*]

[a]*Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Avenida Cuauhtémoc 330, CP 06720, México DF, México*
[b]*Instituto Nacional de Enfermedades Respiratorias, Calzada de Tlalpan 4502, CP 14080, México DF, México*

Received 19 January 2005; accepted 25 April 2005

KEYWORDS
Asthma;
Group A streptococcus;
Scarlatina;
Scarlet fever;
Streptococcus pyogenes

Summary One plausible explanation for the worldwide epidemic increase of asthma prevalence is the hygiene hypothesis, which suggests that better control of infections shifts the immune response toward an allergic phenotype. However, studies demonstrating an inverse association between asthma and infectious diseases are scarce and possess conflicting results. To explore the relationship between asthma and scarlet fever, an ecological analysis of their national trends was carried out. Association of both diseases in their annual (1996–2003), seasonal (by month) and geographic (by state) trends was evaluated using the Spearman's correlation coefficient (r_S). Results showed a strong inverse association between asthma and scarlet fever in all settings. Thus, annual incidence rates of both diseases showed an $r_S = -0.93$ ($P = 0.0009$). Seasonal patterns showed a higher proportion of new asthma cases from September to January, while the number of scarlet fever cases increased from March to June ($r_S = -0.84$, $P = 0.0006$, 1-month lag). Among the 32 Mexican states, the higher the incidence of scarlet fever the lower the incidence of asthma ($r_S = -0.47$, $P = 0.007$). These results suggest that *Streptococcus pyogenes*, the causative agent of scarlet fever, might be one of the major protagonists of the hygiene hypothesis, a possibility deserving of further investigation.
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Introduction

In recent decades, a notable increment in asthma prevalence has occurred in many regions of the world, but to date the cause of this epidemic is largely unknown.[1–3] One of the most plausible explanations is the hygiene hypothesis, which suggests that progressive achievements in the

*Instituto Nacional de Enfermedades Respiratorias, Calzada de Tlalpan 4502, CP 14080, México DF, México.
Tel.: +52 55 5665 0043; fax: +52 55 5665 4623.
E-mail address: mhvargasb@yahoo.com.mx.

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doi:10.1016/j.rmed.2005.04.027

control of infectious diseases among an increasing number of people have predisposed these individuals to the development of an allergic phenotype.[4] This is supposedly based on the reciprocal balance between Th_1 and Th_2 subtypes of T-cells, conditioning that inadequate stimulation of Th_1 responses lead to overproduction of Th_2 T-cell-derived cytokines, which eventually promote the allergic state.[5] Nevertheless, despite its attractiveness this hypothesis is far from being confirmed, and studies demonstrating an inverse relationship between some infectious agents and asthma or atopy remains scarce and with conflicting results.[6–9] In a previous work, we found that medical services for asthma varied greatly among the 32 Mexican states.[10] During this study, we realized that the morbidity rates of nearly all infectious or parasitic diseases either did not correlate at all or showed a tendency to correlate positively with rates of asthma medical services. The only infectious disease that had a negative correlation with asthma and thus supported the hygiene hypothesis was scarlet fever. The more in-deep analysis of a possible relationship between asthma and scarlet fever is the basis of the present report.

Methods

In 1995, asthma became a notifiable disease in Mexico. In the present study, data concerning the number of new cases or incidence rates of asthma and scarlet fever in subjects of all ages were obtained from the website of the Mexican Ministry of Health's Dirección General de Epidemiología.[11] This institution coordinates the registry of 110 diseases, both transmissible and non-transmissible, for which notification is mandatory by law. From all health units providing health services in Mexico ($\sim$17,138 in the year 2000), those actively involved in disease notification increased from approximately 60% in 1995 to $>$90% in 2001. Each week, health units register all new cases of notifiable diseases in an electronic format; this registry is then centralized in the Dirección General de Epidemiología for analysis and diffusion. Quality of information is continuously monitored by specialized staffs who apply corrective measures when needed. Annual trends from 1996 to 2003 were evaluated directly through national incidence rates ($\times$100,000 inhabitants), while seasonal trends (by month) and geographic distribution (by state) were evaluated by averaging number of cases or annual incidence rates, respectively, from the last 5 years of the available period. Statistical evaluation was carried out using the Spearman's correlation coefficient (r_S), while statistical significance was set at two-tailed $P<0.05$.

Results

With respect to time trends, data showed that during the last 8 years asthma incidence rates were relatively stable and with minor changes, from 239.7 in 1996 to 289.1 in 2003. During this same period, time trends of scarlet fever showed a strong negative correlation with respect to asthma, from 15.9 in 1996 to 9.1 in 2003 (Fig. 1A). Correlation between annual incidences of asthma and scarlet fever yielded an $r_S = -0.93$ ($P = 0.0009$).

Regarding seasonal trends, the number of newly diagnosed asthma cases notably increased from September to January, while those corresponding to scarlet fever increased from March to June (Fig. 1B). This inverse pattern had a non-significant correlation with an $r_S = -0.38$. However, when data were re-analyzed with a 1-month lag, the number of scarlet fever cases strongly correlated with the number of asthma cases occurring 1 month later ($r_S = -0.84$, $P = 0.0006$).

Finally, when the geographic relationship between both diseases was explored in all 32 Mexican states, it was apparent that asthma incidence decreased as scarlet fever incidence increased (Fig. 1C), yielding an $r_S = -0.47$ ($P = 0.007$).

Discussion

Although the so-called hygiene hypothesis is an attractive explanation for the recent asthma epidemic, it has not been conclusively demonstrated to date[5] and studies reporting an inverse association between asthma and an infectious disease such as measles and hepatitis remain scarce and with conflicting results.[6–9] Likewise, while some epidemiologic studies have claimed that the history of BCG vaccination was associated with a diminished frequency of asthma, others have been unable to corroborate such an association, and several prospective studies in asthma patients receiving BCG vaccine have yielded inconsistent results.[12–14]

The present work strongly suggests a link between scarlet fever and asthma, though the nature of this association remains to be clarified. An interesting possibility is that *Streptococcus pyogenes*, the causative agent of scarlet fever,

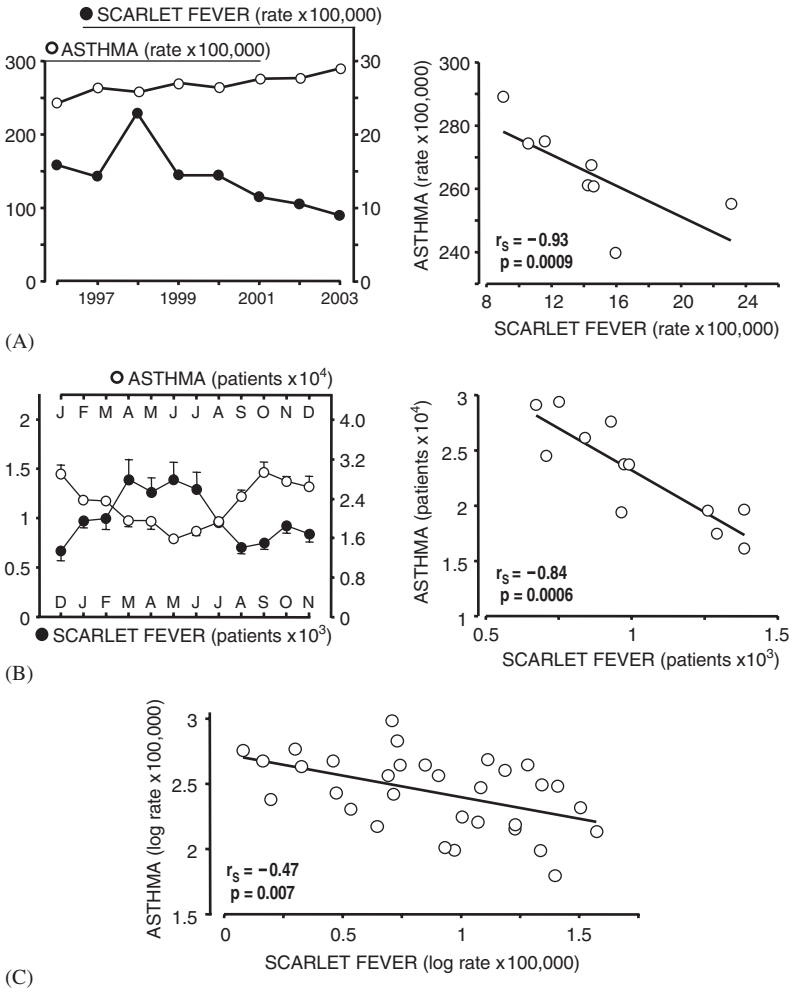

Figure 1 Inverse associations between scarlet fever and asthma in several settings in Mexico. Panel A shows annual incidence rates of both diseases in the last 8 years (left), and the corresponding scatter graph (right). Panel B illustrates seasonal trends (month-by-month) of both diseases after applying a 1-month lag (left), and the corresponding scatter graph (right). In this latter panel, symbols correspond to average and standard error of 5 years (1999–2003). Panel C corresponds to the correlation between incidence rates (average, 1999–2003) of scarlet fever and asthma in the 32 Mexican states.

can prevent the development of the asthmatic process. This microorganism colonizes humans exclusively and can cause a wide range of infections in skin, throat, or other mucosal surfaces and deep tissues. More important, however, is that the prevalence of subjects carrying *S. pyogenes* in pharynx may be as high as 20%.[15] Thus, in the present study incidence of scarlet fever might constitute a surrogate of the carrier-state prevalence in general population.

S. pyogenes is a Gram-positive coccus with some of the most potent superantigens known to date, such as the streptococcal mitogenic exotoxin (SMEZ) and the erythrogenic exotoxins A and C (SPEA and SPEC, respectively).[16] Superantigens cause polyclonal activation of T-cells via their Vβ domain and induce release of a wide array of cytokines.[16,17] Müller-Alouf et al.[18] demonstrated in peripheral blood mononuclear cells cultures that such cytokine release could also be produced by heat-killed streptococci, suggesting that bacteria themselves may evoke this effect via their cell wall components. In this latter study, main cytokines released by SMEZ, SPEA and heat-killed streptococci were IFN-γ (from 600 to 1000-fold the amount released by non-stimulated cells) and IL-12 ($>$200-fold), while the IL-4 increment was negligible. Thus, at least theoretically *S. pyogenes* has the potential to shift the immune status toward a Th_1 response. The possible role of bacterial infections (especially by Gram-positive bacteria) in preventing the development of asthma is in line with studies showing that antibiotic use in the first years of life is accompanied by a higher risk of

subsequent development of asthma,[19,20] and that high concentration of muramic acid in mattress dust is associated with lower prevalence of wheezing in children.[21]

This possible cause–effect relationship between scarlet fever, in the strict sense, or the *S. pyogenes* carrier state, in the broad sense, and asthma protection deserves to be fully explored, though alternative explanations (e.g., that asthma diminishes the infectivity or pathogenicity of *S. pyogenes*, or that asthma and scarlet fever are independent diseases related to a third factor) should also be considered and further investigated.

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